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ORIGINAL ARTICLES

Jaundice in Early Infancy	<i>J. A. M. White</i>	583
Cushing's Syndrome in Childhood	<i>Bernard Zilberg</i>	589
Echo Virus Type 9	<i>J. Melvin</i>	594
Melanosis—A Peculiar Dermatoses in the African	<i>Michael Gelfand</i>	595
The Use of Hypothermia in Neurosurgery	<i>N. J. Micklem and G. V. S. Wright</i>	599
Problems in Acute Head Injuries	<i>R. A. Fleming</i>	603
Evaluation of Antibiotics in Urinary Infections	<i>I. Langdale Gregory and J. McDonnell</i>	618

EDITORIALS

The Association of Bilharziasis and Malignant Disease in the Urinary Bladder	623
Report of the Medical Research Council for the Year 1957-58	624
Health Checks	625
A Gift of Pictures from Lady Chancellor	626
An Account of a Dominican Nurse's Travels to Mashonaland in 1892	627
The Scope of Silicosis Compensation in S. Rhodesia by M. I. Hirsch	629
Sir Russell Brock Visits Salisbury	631
Cardiac Surgery	631
Mindolo Centre for Blind Africans	634
Correspondence	635
The Harare Hospital Staff Round	636
Book Reviews	641
Medical Council of S. Rhodesia	643
The Pharmaceutical Society of Rhodesia and Nyasaland	645
Latest Pharmaceutical Preparations	648

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The Clinical Picture of Cushing's Syndrome in Childhood

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The adrenal cortex produces the following groups of hormones: androgens, glucocorticoids (cortisol), mineralocorticoids (aldosterone) and oestrogens. Hyperadrenocorticism results in a number of different clinical syndromes, depending upon which of the various groups of steroids are in excess.

1. The adrenogenital syndrome is due to excessive androgen secretion and may be either congenital or acquired. The congenital variety is almost invariably the result of adrenal hyperplasia. When it occurs in the female it leads to varying degrees of pseudo-hermaphroditism (female intersexuality) with progressive virilization. In the male it leads to macrogenitosomia praecox. The condition is characterised by an excessive secretion of 17-ketosteroids and, in a considerable percentage of cases, this is accompanied by a deficient secretion of glucocorticoids and mineralocorticoids. When the hyperplasia arises after birth it leads to virilism in the female and precocious sexual development in the male.

2. Cushing's syndrome is due to over-production of glucocorticoids. It is characterised by obesity, plethora, purple cutaneous striae, hypertension, hyperglycaemia and occasionally osteoporosis.

3. Primary aldosteronism or Conn's syndrome is due to excessive production of mineralocorticoids. It is characterised by intermittent muscular pains, cramps, weakness, paralyses and hypertension. Renal dysfunction occurs and tetany may be a feature. The blood shows hypokalaemia, hypernatraemia and alkalosis. Conn's syndrome has not been recorded in childhood.

4. Feminizing adrenal tumour produces its effects by excessive secretion of oestrogen. Twelve cases of such tumours producing gynaecomastia in males have been reported (Wilkins, 1950).

In childhood the adrenogenital syndrome is the commonest manifestation of hyperadrenocorticism, while Cushing's syndrome is the next in frequency. In infancy and early childhood

practically all cases of Cushing's syndrome are due to carcinoma of the adrenal, whereas over the age of ten adrenal hyperplasia becomes a more common cause of the syndrome (Wilkins, 1950). One case of Cushing's syndrome in childhood due to nodular hyperplasia has been reported (Chute *et al.*, 1949) and Powell *et al.* (1955) have recorded a case due to bilateral cortical adenomas. As in adults, the syndrome is commoner in females. Because carcinomas are biochemically pluripotent, they may secrete excessive quantities of androgens, glucocorticoids, oestrogens and aldosterone where measured (Jackson, Zilberg, Lewis and McKenzie, 1958). Thus, in cases of carcinoma, the clinical picture is a mixed one, combining features of Cushing's syndrome and the adrenogenital syndrome.

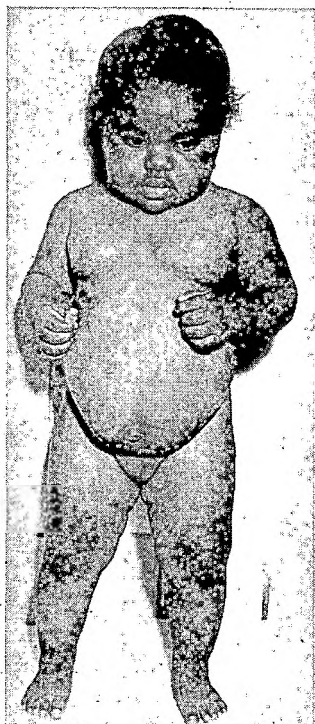
BASIS FOR THE CLINICAL PICTURE

Increased secretion of glucocorticoids may give rise to obesity, retarded growth, muscular weakness, friability of capillaries and skin, with resulting striae, osteoporosis and a diabetic sugar curve. The excessive mineralocorticoids are responsible for hypertension, increased blood volume and serum sodium, with decreased serum potassium. Androgens are responsible for hirsutism, acne and decreased ovarian function. In boys there is precocious development of secondary sex characteristics. In several cases precocious breast development and menstrual bleeding occur, indicating oestrogen excess. The variations in the symptoms in different patients can be explained by differences in the relative amounts of the three groups of hormones which are secreted. In some ways androgens and glucocorticoids are mutually antagonistic, so that in some cases bone age, bone density and blood sugar may be normal.

THE CLINICAL PICTURE OF CUSHING'S SYNDROME IN CHILDHOOD

In infancy the presenting symptoms are usually obesity, acne, seborrhoea and hirsuties. Moon facies, a ruddy complexion and the "buffalo neck" may be striking. The obesity is usually more generalised than in adult cases. In the female some clitoral enlargement may be found. Striae are not common. Hypertension and a diabetic glucose tolerance curve are sometimes present.

In older children, in addition to the above features, pain in the back due to osteoporosis is often striking. Striae due to rapidly developing obesity may be marked. The patients are usually shorter than the average for their age.



BEFORE ADRENALECTOMY



← Figs. 1 (a) and 1 (c) (Case 1).

Fig. 1 (c). →

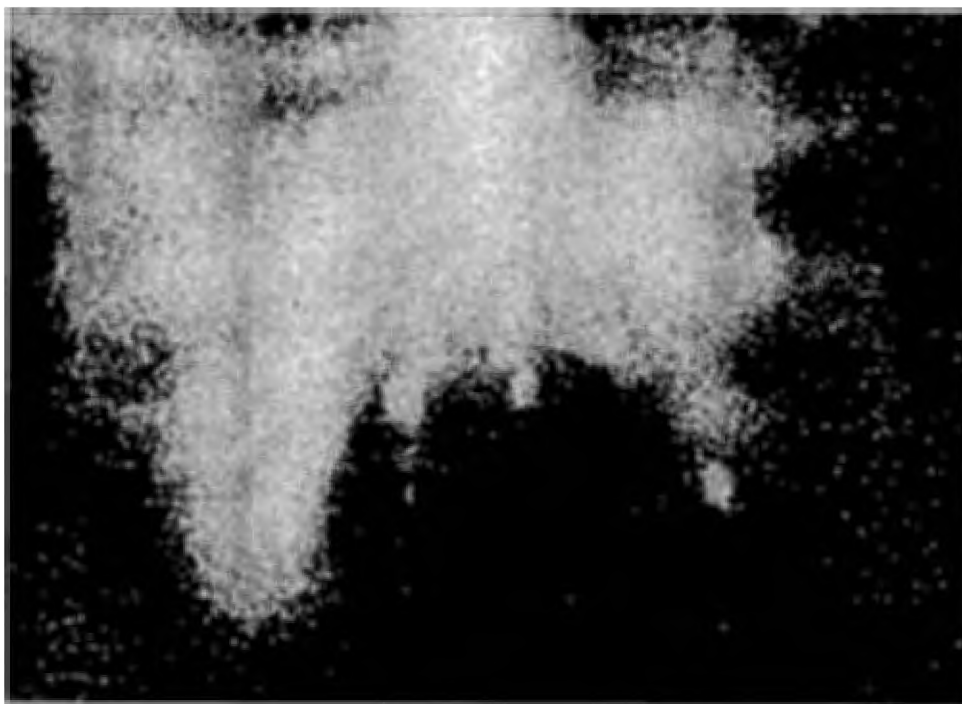


Fig. 2 (Case 1)—Tomographic view of intravenous pyelogram, showing depressed left kidney with tumour outlined above it.

AFTER ADRENALECTOMY



Figs. 1 (b) and 1 (d) (Case 1). Appearance 12 weeks after removal of adrenal tumour (adrenalectomy by Professor J. H. Louw, Cape Town).



Fig. 3 (Case 1)—Left adrenal gland after removal.

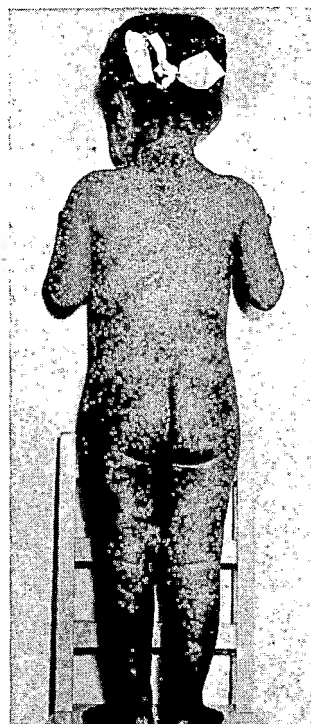


Fig. 1 (d).

Case 1.—Coloured girl, aged 2½ years. Abnormally rapid gain in weight and development of pubic and axillary hair since age of one year. Typical Cushing-like facies and build. Signs of virilism. B.P. 130/90 (Normal $99 \pm 25/64 \pm 25$). Fasting blood sugar 88 mg./100 ml. (normal 75-95 mg./100 ml.). Bone age normal.

Twenty-four-hour urinary output of 17 ketosteroids 39 mg. (normal for this age, under 2 mg.); 17 ketogenic steroids 11.6 mg. (normal under 3 mg.) and aldosterone 75 µg (normal under 10 µg). Fractionation of the 17 ketosteroids showed an abnormal amount of dehydroepiandrosterone. Raised plasma cortisol levels. Left-sided adrenal carcinoma removed at operation (Prof. J. H. Louw).

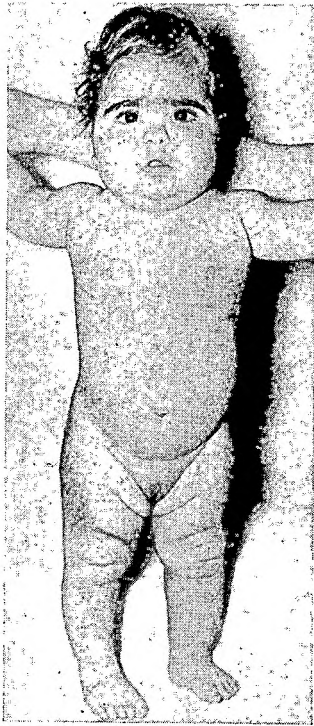


Fig. 4 (a) (Case 2).



Fig. 4 (b) (Case 2).—Appearance 10 weeks after removal of left-sided adrenal carcinoma (Prof. J. H. Louw).

Case 2.—European girl, aged one year. Rapid development of generalised hirsuties and rash on forehead since age of eight months. Typical Cushing-like facies and build. Acneform facial eruption and signs of virilism. B.P. 120/100 (normal $96 \pm 30/66 \pm 25$). Fasting blood sugar 125 mg./100 ml. Normal bone age.

Twenty-four-hour urinary output of 17 ketosteroids 4.9 mg. (normal for this age, under 1 mg.). Fractionation of the 17 ketosteroids did not show an excessive amount of dehydroepiandrosterone. Biochemical findings were not strongly suggestive of carcinoma and intravenous pyelography did not localise the lesion. At operation (Prof. J. H. Louw), a left-sided adrenal carcinoma was found and removed.

Radiographs may show osteoporosis. Due to demineralization and loss of calcium, renal calculi may develop. Signs of virilism are usually less marked than in the adrenogenital syndrome.

DIAGNOSIS

The diagnosis is made by recognising the characteristic clinical features. Confirmation is obtained by finding a high urinary secretion of 17-ketogenic steroids (which largely represent metabolites of cortisol) and a raised plasma cortisol level. The output of 17-ketosteroids is usually raised, and when this is very high it suggests adrenal carcinoma as the basis of the syndrome. Carcinoma is probably present when fractionation of the 17-ketosteroids reveals a large quantity of dehydroepiandrosterone. Adrenal hyperplasia is suggested when the output of 17-ketosteroids rises markedly after the administration of A.C.T.H. Intravenous pyelography and presacral air insufflation may localise an adrenal tumour by showing depression of the kidney on the affected side. The final decision about the nature and site of the lesion is made at operation. In hyperplasia, both glands are enlarged. If a functioning tumour is present the opposite gland undergoes atrophy. The type of lesion can therefore be determined when the first gland is exposed. A tumour is obvious on inspection. If the gland is large but no tumour is present, it can be assumed that hyperplasia is the cause. If the gland is small the opposite adrenal is the site of tumour (carcinoma or adenoma).

TREATMENT

In the case of adenoma or carcinoma (providing there are no metastases) the offending adrenal is removed. Cortisone is given pre-operatively and continued for a few days post-operatively, when it is gradually withdrawn.

A.C.T.H. is given at this stage to stimulate the remaining adrenal. If hyperplasia is present, total bilateral adrenalectomy is performed. Substitution therapy with cortisone is then continued permanently.

SUMMARY

(1) In children under the age of ten, Cushing's syndrome is almost invariably due to adrenal carcinoma. After this age, adrenal hyperplasia becomes an important cause.

(2) Carcinomas are biochemically pluripotent with the result that the syndrome is a mixed one, combining features of Cushing's and the adrenogenital syndrome.

(3) Markedly raised urinary levels of 17-ketosteroids and dehydroepiandrosterone are suggestive of adrenal carcinoma.

(4) Biochemical and hormonal studies may give conflicting results. The final diagnosis can only be made at operation.

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Acknowledgments

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